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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,696	01/19/2001	Daniel S. Sem	P-TB 4567	6467

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EXAMINER	
BAKER, MAURIE GARCIA	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 12/18/2002

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/765,696	Sem
Examiner	**Art Unit**
Mauri G. Baker, Ph.D.	1639

-- The MAILING DATE of this communication app ars on th cov r sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 30, 2002*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-9, 11-14, and 37-43* is/are pending in the applica

4a) Of the above, claim(s) *1-8 and 38-40* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *9, 11-14, 37, and 41-43* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Please note: The number of Art Unit 1627 has been changed to 1639. Please direct all correspondence for this case to **Art Unit 1639.**

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

2. The Response filed October 30, 2002 (Paper No. 22) is acknowledged. Claims 9, 11-14 and 37 were amended, claims 38-43 were added and no claims were cancelled. Therefore, claims 1-9, 11-14 and 37-43 are pending.

3. This application contains claims 1-8 drawn to an invention nonelected with traverse in Paper No. 8. Thus, these claims are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

4. Newly submitted claims 38-40 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons.

5. Claims 38-40 are drawn to a different invention than the one currently under examination with respect to common ligands that compete for cofactor binding. The claims previously under examination recited that the "common ligand binds to a cofactor binding site". There was nothing present in the previously examined claims with respect to competitive binding. Thus claims 38-40 are different in scope and represent an invention that is independent or distinct from the invention originally claimed.

6. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 38-40 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

7. Claims 9, 11-14, 37 and 41-43 are examined on the merits in this action.

Withdrawn Rejections

8. The previous rejections under 35 USC 112, first paragraph are withdrawn in view of applicant's amendments. Additionally, the previous rejection under 35 USC 103 is withdrawn and new rejections under 35 USC 103 are set forth below.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 9, 11-14, 37 and 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over He et al (On PTO-1449; Bioorg. Med. Chem. Lett., 1994) in view of Traxler et al (On PTO-1449; J. Med. Chem., 1991).

The following interpretations are used for this rejection:

The specification defines a population as "a group of two or more different molecules" (page 14, line 4). He et al teach making two or more different molecules that comprise a common ligand (an ATP mimic; reading on the claimed "cofactor or mimic thereof") and a specificity ligand linked by a linker. The specificity ligand of He et al reads on the claimed "second ligand". As taught by the reference, these ligands can bind at least 2 different receptors from the same family (kinases) which bind ATP as a cofactor (reading on instant claims 11-12 and also limitation in claim 41 with respect to "two or more enzymes that bind to the same cofactor"). The linker in the compounds of He et al is a simple methylene chain of variable length and as such would comprise a linker possessing perfect C2 symmetry as defined in the specification on page 10 (claims 13-14 and 42-43).

Specifically, He et al discuss the fact that kinases have two binding sites in the catalytic domain; one of these sites binds ATP while the other binds peptidic substrates (page 2845). He et al disclose making bisubstrate inhibitors "suitable to interact simultaneously with the ATP and the protein substrate binding domains" (page 2845, 2nd

paragraph). The compounds contain an ATP mimic that would comprise the common ligand that is a "cofactor or mimic thereof". These compounds are of the general structure shown in Figure 2, with specific examples in Table 1. This ligand (ATP mimic) plus the methylene chain linker read on the claimed "module", with the different second ligands of He reading on the "second ligand" of the instant claims. He et al teach second ligands that are either an amine or an amino acid. The second ligand creates differences in the binding of the compounds with two different kinases, protein kinase C (PKC) and c-AMP dependent protein kinase, as shown in Table 1. Changes in this second ligand are made due to differences in the binding sites of the two different kinases (page 2849), reading on different receptors in the "receptor family" of kinases.

He et al lack the specific teaching of identifying ligands that have *specificity for* a second and/or third receptor in the receptor family as the compounds of the reference only show specificity for PKC. However, it is noted that the "population" of compounds taught by He et al meets all of the limitations of the claimed "population of bi-ligands" and that there are a wide variety of different kinases known in the art (see Traxler et al, for example, described below) that were not specifically tested by He et al. The properties of a compound are intrinsic to its structure and thus the "population" of compounds taught by He et al, having all of the claimed limitations, would also implicitly have the same binding characteristics. The instant claims contain ***no*** specific structural limitations whatsoever and the compounds of He et al meet the functional limitations of the claims.

Furthermore, the synthesis of bisubstrate inhibitors for enzymes was extremely well established at the time of the invention. This is shown by the teachings of Traxler et al, for example. This reference also teaches bisubstrate inhibitors of kinases (see Abstract, Table I and section entitled "Concept and Design of Inhibitors"). The bisubstrate inhibitors of Traxler et al ***do*** show specificity for more than one enzyme in the kinase family, see Table II. The reference also teaches that a variety of kinases have known and distinct substrate specificities and that with this knowledge, "design of selective inhibitors of this class of enzymes should be possible" (page 2328). Traxler et al also teach that "bisubstrate inhibitors ...have the potential for high selectivity and potency" (page 2328, 2nd column).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to perform the method of He et al to identify ligands that have specificity for a second and/or third receptor in the receptor family, in view of the teachings of Traxler et al. The general conditions of identifying bisubstrate inhibitors "suitable to interact simultaneously with the ATP and the protein substrate binding domains" of kinases was well-known as taught by He et al. One of ordinary skill would have been motivated to create different bisubstrate inhibitors because the similarity between the structures and properties is sufficiently close that one of ordinary skill would have been motivated to make additional inhibitors in searching for more potent compounds. As taught by Traxler et al, once the substrate specificity of an enzyme is known, it is obvious to design new bisubstrate inhibitors based on this knowledge and "bisubstrate inhibitors ...have the potential for high selectivity and potency". One of

ordinary skill would also have had a reasonable expectation of success based on the fact that He et al teaches the synthesis of such inhibitors reading directly on those of the instant claims.

11. Claims 9, 11-14, 37 and 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over He et al (On PTO-1449; Bioorg. Med. Chem. Lett., 1994) in view of Traxler et al (On PTO-1449; J. Med. Chem., 1991) and Rossman et al (On PTO-1449; The Enzymes, 3rd Ed. 1975) and Radzicka et al (On PTO-1449; Methods Enzymol., 1995).

The following rejection applies to the elected species of dehydrogenase and nicotinamide adenine dinucleotide.

The following interpretations are used for this rejection:

The specification defines a population as "a group of two or more different molecules" (page 14, line 4). He et al teach making two or more different molecules that comprise a common ligand (an ATP mimic; reading on the claimed "cofactor or mimic thereof") and a specificity ligand linked by a linker. The specificity ligand of He et al reads on the claimed "second ligand". As taught by the reference, these ligands can bind at least 2 different receptors from the same family (kinases) which bind ATP as a cofactor (reading on instant claims 11-12 and also limitation in claim 41 with respect to "two or more enzymes that bind to the same cofactor"). The linker in the compounds of He et al is a simple methylene chain of variable length and as such would comprise a linker possessing perfect C2 symmetry as defined in the specification on page 10 (claims 13-14 and 42-43).

Specifically, He et al discuss the fact that kinases have two binding sites in the catalytic domain; one of these sites binds ATP while the other binds peptidic substrates (page 2845). He et al disclose making bisubstrate inhibitors "suitable to interact simultaneously with the ATP and the protein substrate binding domains" (page 2845, 2nd paragraph). The compounds contain an ATP mimic that would comprise the common ligand that is a "cofactor or mimic thereof". These compounds are of the general structure shown in Figure 2, with specific examples in Table 1. This ligand (ATP mimic) plus the methylene chain linker read on the claimed "module", with the different second ligands of He reading on the "second ligand" of the instant claims. He et al teach second ligands that are either an amine or an amino acid. The second ligand creates differences in the binding of the compounds with two different kinases, protein kinase C (PKC) and c-AMP dependent protein kinase, as shown in Table 1. Changes in this second ligand are made due to differences in the binding sites of the two different kinases (page 2849), reading on different receptors in the "receptor family" of kinases.

He et al lack the specific teaching of identifying ligands that have *specificity for* a second and/or third receptor in the receptor family as the compounds of the reference only show specificity for PKC. However, it is noted that the "population" of compounds taught by He et al meets all of the limitations of the claimed "population of bi-ligands" and that there are a wide variety of different kinases known in the art (see Traxler et al, for example, described below) that were not specifically tested by He et al. The properties of a compound are intrinsic to its structure and thus the "population" of compounds taught by He et al, having all of the claimed limitations, would also implicitly

have the same binding characteristics. The instant claims contain ***no*** specific structural limitations whatsoever and the compounds of He et al meet the functional limitations of the claims.

Furthermore, the synthesis of bisubstrate inhibitors for enzymes was extremely well established at the time of the invention. This is shown by the teachings of Traxler et al, for example. This reference also teaches bisubstrate inhibitors of kinases (see Abstract, Table I and section entitled "Concept and Design of Inhibitors"). The bisubstrate inhibitors of Traxler et al ***do*** show specificity for more than one enzyme in the kinase family, see Table II. The reference also teaches that a variety of kinases have known and distinct substrate specificities and that with this knowledge, "design of selective inhibitors of this class of enzymes should be possible" (page 2328). Traxler et al also teach that "bisubstrate inhibitors ...have the potential for high selectivity and potency" (page 2328, 2nd column).

With respect to the elected species of dehydrogenase and nicotinamide adenine dinucleotide, the following is noted. Rossman et al teach that dehydrogenases bind nicotinamide adenine dinucleotide as a cofactor and that that a variety of structures of dehydrogenase enzymes are known (see, for example, page 64 and page 70). The reference also teaches that there is structural similarity between dehydrogenases and kinases (see section 2, pages 96-98). Also, Radzicka et al teach that "transition state and multisubstrate inhibitors have been prepared against enzymes catalyzing reactions of every class" (page 288) and that such molecules "may express a large entropic advantage in binding" (page 287).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to perform the method of He et al to identify ligands that have specificity for a second and/or third receptor in the receptor family, when the family is dehydrogenases binding nicotinamide adenine dinucleotide, in view of the teachings of Traxler et al, Rossman et al and Radzicka et al. The general conditions of identifying bisubstrate inhibitors "suitable to interact simultaneously" two sites of an enzyme was well-known as taught by He et al and also Radzicka et al. Radzicka et al teach that "transition state and multisubstrate inhibitors have been prepared against enzymes catalyzing reactions of every class". One of ordinary skill would have been motivated to create different bisubstrate inhibitors because the similarity between the structures and properties is sufficiently close that one of ordinary skill would have been motivated to make additional inhibitors in searching for more potent compounds. As taught by Traxler et al, once the substrate specificity of an enzyme is known, it is obvious to design new bisubstrate inhibitors based on this knowledge and "bisubstrate inhibitors ...have the potential for high selectivity and potency". Moreover, Rossman et al teach that there is structural similarity between dehydrogenases and kinases, thus the application of the method of He et al to the dehydrogenase family would be obvious to one of ordinary skill.

Response to Arguments

12. Applicant's arguments filed October 30, 2002 have been fully considered but are moot in view of the new grounds of rejection set forth above. It is noted that it was previously stated that

the elected species was free of the art; however, due to applicant's claim amendments and reconsideration of the instant case, the elected species is rejected as set forth above.

Status of Claims/ Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie Garcia Baker, Ph.D. whose telephone number is (703) 308-0065. The examiner can normally be reached on Monday-Thursday and alternate Fridays from 8:30 to 6:00.

15. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maurie Garcia Baker, Ph.D.
December 12, 2002

MAURIE GARCIA BAKER, Ph.D.
PATENT EXAMINER